Animal Behaviour xxx (2015) 1–9

Contents lists available at ScienceDirect

Animal Behaviour

journal homepage: www.elsevier.com/locate/anbehav

Special Issue: Social Evolution

Genetic influences on social attention in free-ranging rhesus macaques

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ARTICLE INFO

Article history:
Received 5 January 2015
Initial acceptance 19 January 2015
Final acceptance 9 February 2015
Available online xxx
MS. number: SI-15-00007

Keywords:
Macaca mulatta
neuroethology
primate
rhesus macaque
serotonin pathway
social attention
TPH2
vigilance

An ethological approach to attention predicts that organisms orient preferentially to valuable sources of information in the environment. For many gregarious species, orienting to other individuals provides valuable social information but competes with food acquisition, water consumption and predator avoidance. Individual variation in vigilance behaviour in humans spans a continuum from inattentive to pathological levels of interest in others. To assess the comparative biology of this behavioural variation, we probed vigilance rates in free-ranging macaques during water drinking, a behaviour incompatible with the gaze and postural demands of vigilance. Males were significantly more vigilant than females. Moreover, vigilance showed a clear genetic component, with an estimated heritability of 12%. Monkeys carrying a relatively infrequent 'long' allele of *TPH2*, a regulatory gene that influences serotonin production in the brain, were significantly less vigilant compared to monkeys that did not carry the allele. These findings resonate with the hypothesis that the serotonin pathway regulates vigilance in primates and by extension provoke the idea that individual variation in vigilance and its underlying biology may be adaptive rather than pathological.

For group-living animals, survival and reproductive success often depend on the appropriate perception of others and adaptive responses to their behaviour. Better information permits better informed action, thus endorsing the hypothesis that the brain has been shaped by natural selection to facilitate acquisition of information about the identity, behavioural states and impending behaviours of others (Allman, 2000; Dunbar, 1998). Vigilance behaviour, visual scanning of the external environment, has been documented in dozens of different species of mammal and bird (Elgar, 1989). Although vigilance can be used to detect predators (Elgar, 1989; Roberts, 1996), it can also be used to gather social information (Chang et al., 2013; Klein, Shepherd, & Platt, 2009). Some gregarious species, like many primates, reduce predation risk by living in groups, but consequently face elevated levels of competition with conspecifics. In these animals, gathering social information may be the primary function of visual monitoring (Chance & Jolly, 1970; Treves, 2000).

Consistent with this idea, recent studies have demonstrated that ringtail lemurs, *Lemur catta* (Shepherd & Platt, 2008), rhesus macaques, *Macaca mulatta* (Deaner, Khera, & Platt, 2005) and humans (Hayden, Parikh, Deaner, & Platt, 2007) value the opportunity to acquire information about conspecifics. For rhesus macaques, the value of information about the dominance status and reproductive quality of others can substitute for fluid or food rewards (Deaner et al., 2005; Watson, Ghodasra, & Platt, 2009), and for human males the value of information about the attractiveness of females

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http://dx.doi.org/10.1016/j.anbehav.2015.02.012

can substitute for money and time, and can motivate work (Hayden et al., 2007). Moreover, wild primates routinely attend to the social interactions of others, and orient visually towards conspecific calls in playback experiments (e.g. Bergman, Beehner, Cheney, & Seyfarth, 2003; Cheney & Seyfarth, 1999; Cheney, Seyfarth, & Silk, 1995). These experiments also demonstrate that recent social interactions influence the selectivity of this orienting behaviour, indicating that nonhuman primates remember interactions with opponents and allies and use this information to modulate attention (Cheney, Moscovice, Heesen, Mundry, & Seyfarth, 2010; Engh, Hoffmeier, Cheney, & Seyfarth, 2006; Wittig, Crockford, Langergraber, & Zuberbühler, 2014; Wittig, Crockford, Seyfarth, & Cheney, 2007; Wittig, Crockford, Wikberg, Seyfarth, & Cheney, 2007).

Consonant with these behavioural studies, specialized populations of neurons in brain areas linked to attention (Klein, Deaner, & Platt, 2008), self-control (Ebitz & Platt, 2015) and reward (Klein & Platt, 2013; Watson & Platt, 2012) respond when monkeys have the opportunity to acquire information about others or use this information to guide subsequent visual exploration behaviour (Shepherd, Klein, Deaner, & Platt, 2009). Some of these same structures are also activated in humans when they choose to acquire visual information about others at the expense of monetary rewards (Smith et al., 2010) or effortful labour (Aharon et al., 2001). Together, these observations resonate with the idea that the challenges of social life favoured the evolution of specialized neural circuits mediating the acquisition and utilization of information about other individuals, which evolved from basal circuits mediating information acquisition and utilization in nonsocial contexts (Adams, Watson, Pearson, & Platt, 2012; Chang et al., 2013; Pearson, Watson, & Platt, 2014).

Despite the clear adaptive value of social vigilance, and clear evidence that specific neural circuits have evolved to support this behaviour, individuals often vary substantially in social attention behaviour (Frischen, Bayliss, & Tipper, 2007; Seyfarth & Cheney, 2013; Shepherd, Deaner, & Platt, 2006). The sources and persistence of these differences remain to be understood fully, but some seem to be genetic in origin (Constantino & Todd, 2000; Ebstein, Israel, Chew, Zhong, & Knafo, 2010; Jamain et al., 2008). In many animals, including mammals, crustaceans and fish, serotonin regulates social behaviour, including aggression and dominance relationships (Edwards & Kravitz, 1997; Higley et al., 1996, 1992). Among primates, in particular, serotonin influences a broad array of social functions (Watson et al., 2009). Indeed, the human psychiatric literature is replete with associations between genetic variation in the serotonin system and behavioural pathology (Caspi, Hariri, Holmes, Uher, & Moffitt, 2010; Caspi et al., 2003; Hariri et al., 2005).

Two important proteins in the serotonin system are the serotonin transporter (5-HTT), which removes serotonin from the synaptic space between neurons in the brain, and tryptophan hydroxylase (TH), the enzyme that regulates serotonin production. The genes encoding these two proteins have been repeatedly, although controversially, linked to various psychiatric disorders in humans (Canli, Congdon, Todd Constable, & Lesch, 2008; Gao et al., 2012; Hariri et al., 2005; Hariri & Holmes, 2006; Popova & Kulikov, 2010; Waider, Araragi, Gutknecht, & Lesch, 2011; Zhou et al., 2005) and influence anxiety-related personality traits among healthy individuals (Gutknecht et al., 2007; Lesch et al., 1996; Reuter, Kuepper, & Hennig, 2007; Sen, Burmeister, & Ghosh, 2004).

One well-studied polymorphism in the gene encoding the serotonin transporter is the 5-HTT length polymorphic region (5-HTTLPR), which consists of a repeating sequence of base pairs. There are two predominant alleles in the human population: the short allele, which has 14 repeat elements, and the long allele, which has 16 (Hariri & Holmes, 2006). The short allele is typically associated with psychiatric disease, anxiety-related traits and activity in the amygdala, a brain region associated with threat detection and vigilance (Hariri et al., 2005; Hariri & Holmes, 2006; Hariri et al., 2002). An orthologous repeat 5-HTTLPR variant exists in rhesus macaques (Canli & Lesch, 2007), and in this manuscript we refer to both human and rhesus polymorphisms as 5-HTTLPR. Rhesus macaques who carry at least one copy of the less common short allele and who are exposed to a stressful period during early development (peer rearing versus maternal rearing), show delayed neural development, impaired serotonergic function, higher aggression and higher stress hormone levels than monkeys who carry two copies of the long 5-HTTLPR allele (Barr et al., 2004; Bennett et al., 2002; Champoux et al., 2002). Moreover, monkeys carrying the short 5-HTTLPR allele are more likely to avoid dominant faces in an attention task, show suppressed risk taking after exposure to dominant faces and have greater physiological arousal in response to dominant faces (Watson et al., 2009). Altered social reactivity in macaques carrying the 5-HTTLPR short allele is consistent with functional imaging studies in humans, in which the short 5-HTTLPR allele is linked to greater amygdala activity when viewing angry faces (Hariri et al., 2005, 2002).

The TPH2 enzyme is another important regulator of serotonergic function and there exist several polymorphisms in the human TPH2 gene (Gao et al., 2012; Popova & Kulikov, 2010). Unlike 5-HTTLPR, there is no single TPH2 polymorphism that has been particularly well studied or characterized, although several are linked to psychiatric disease, altered amygdala activity and anxiety-related personality traits in a manner similar to 5-HTTLPR (Popova & Kulikov, 2010). In the current study we focus on a rhesus-specific polymorphism, referred to here as the TPH2 insertion polymorphism (TPH2IP), in which 159 additional base pairs are inserted into the untranslated region at the terminal end of the gene (Chen, Novak, Hakim, Xie, & Miller, 2006). Alleles associated with TPH2IP are either long (i.e. with insertion) or short (without insertion); the short allele is more common (80% frequency in captive rhesus macaques; Chen et al., 2006).

The precise influence of these polymorphisms on serotonin in vivo remains mysterious. In vitro assays suggest the short 5-HTTLPR and TPH2IP alleles decrease expression of 5-HTT and TPH2, respectively (Bennett et al., 2002; Chen et al., 2006; Greenberg et al., 1999; Heils et al., 1996), which should theoretically increase the amount of circulating 5-HT in both cases. This increase in 5-HT may eventually be downregulated or stabilized via compensatory mechanisms, such as negative feedback loops mediated by the 5-HT1a receptor (Christian et al., 2013). In support of this hypothesis, a study in mice found that a TPH2 polymorphism altered 5-HT synthesis rate, affected anxiety-related behaviours and desensitized 5-HT1a receptors, but did not alter brain serotonin concentration (Berger et al., 2012). Similarly, there is no association between 5-HTTLPR genotype and the level of 5HTT density as measured by positron emission tomography in adult humans (PET) (Kobiella et al., 2011; Shioe et al., 2003; Willeit et al., 2001), although amygdala volume and 5-HT1a receptor binding both vary with this genotype (Kobiella et al., 2011, page 102; David et al., 2005, page 144). Genetic variation in both TPH2 and 5-HTT may shape the brain during development (Berger et al., 2012; Kobiella et al., 2011), consistent with observations that psychiatric disease emerges from the interaction of childhood and serotonin genotype (reviewed in Caspi et al., 2010; Hariri & Holmes, 2006).

Although precisely how genetic variation in the serotonergic system influences neural circuit function remains unclear, this variation is capable of shaping behavioural phenotypes. For example, both 5-HTTLPR and TPH2IP influence affiliative behaviours in free-ranging rhesus macaques (Brent et al., 2013).

Please cite this article in press as: Watson, K. K., et al., Genetic influences on social attention in free-ranging rhesus macaques, Animal Behaviour (2015), http://dx.doi.org/10.1016/j.anbehav.2015.02.012